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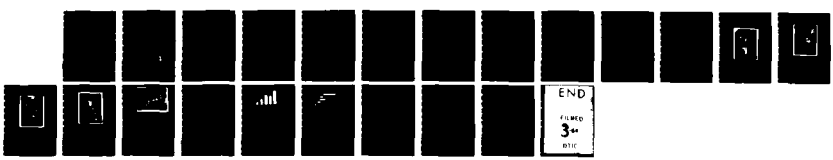

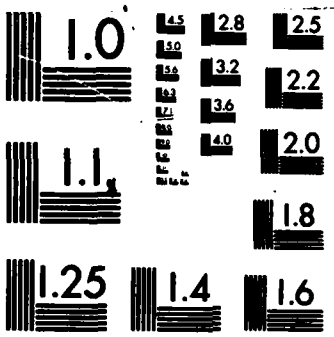

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COMPUTER ASSISTED CYTOLOGIC ASSESSMENT

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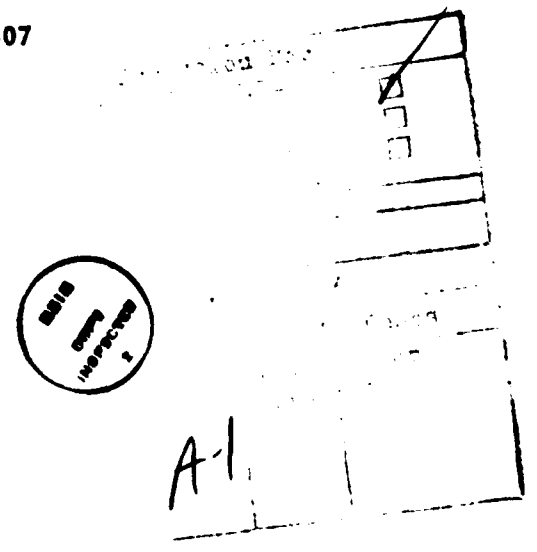


ABSTRACT

Cytology is the assessment of cellular detail that may be accomplished in a rapid and expedient manner. A criterion used for cytologic evaluation of cells consists of a comparison of the ratio of the nucleus to the cytoplasm. It was the purpose of this study to determine if microscopic measurements of a cell's nuclear and cytoplasmic areas could provide an accurate and precise means for determining cytologic status. Oral cytologic specimens were stained by the Papanicolaou method and were assessed by three pathologists using conventional light microscopy. Specimens were classified into categories I through V, ranging from normal epithelial cells (I) to malignant cells (V). There were at least ten specimens for each category. A Zeiss Image Analysis System with an LED cursor and digitizer tablet were then utilized to trace fifty epithelial cells from each of the ten slides taken from each category. A total of 2500 measurements were performed in approximately four hours. A nuclear to cytoplasmic ratio was derived that was unique and specific for four of the five cytology categories. It was concluded from this study that a computer-assisted technique for cytologic evaluation of oral epithelial cells based upon a nuclear to cytoplasmic ratio is both feasible and practical.

INTRODUCTION

Cytology is the science of rapidly screening cells for the detection of atypia that can be associated with premalignant or malignant conditions. The cytologist assesses the global appearance of a large number of cells for nuclear to cytoplasmic relationships, general morphologic characteristics, hyperchromatism, etc. Classification of the cells being scrutinized is based, therefore, on the cytologist's overall impression of the specimen.

Cytology is frequently used for the evaluation of oral epithelium (Bernstein and Miller, 1975). A tongue depressor or other rigid device is used to retrieve a sufficient cell population that can be appropriately stained. Classification of the cells may fall into one of five categories: Class I - normal; Class II - normal, some atypia; Class III - uncertain, borderline changes are evident; Class IV - possible cancer, uncertainty remains; Class V - positive for cancer.

Although King, Jr. (1971) states that the oral cytology technique is the best method available for early detection of oral cancer, several authors do not advocate the oral cytology technique (Ingram et al., 1964; Shapiro et al., 1964; Rovin, 1971).

The subjective nature of the cytologic assessment can be reduced by using a quantitative technique. A computer-assisted image analysis system is a means for performing a quantitative evaluation of a cytologic specimen. Bartels et al. (1974, 1975) used a computer for

analysis and discrimination between different cell types. Koss et al. (1975) analyzed single endothelial cell images with a computer to detect atypia associated with urothelial cancer. Flow cytometry is another example of a computerized analysis system that has become widely used as a diagnostic technique. A computer image analysis system was employed in this study to determine nuclear to cytoplasmic ratios of previously classified oral cytologic specimens using conventional methods.

METHODS AND MATERIALS

The cytology specimens were collected with a tongue depressor or metallic instrument by manually scraping the area of interest, smearing the collected cells onto a microscope slide, fixing in 95% ethanol for 15 minutes, air-drying, and staining by the Papanicolaou method. The processed slides were then classified by three oral pathologists into one of the five classes, i.e., Class I, II, III, IV, or V (Figure 1).

Ten specially coded microscopic slides were available for each class. A Zeiss 64K CP/M computer was employed by one of the authors (MLB) to evaluate all the slides in a blind fashion. Using an LED cursor on a digitizer tablet, each cell's nucleus and cytoplasmic peripheries were traced (Figure 2).

From each of the 50 slides, 50 cells were analyzed and a nuclear to cytoplasmic ratio was derived. The slides were then identified according to their code. A value (the ratio) for each cell's nuclear

to cytoplasmic ratio was then compared with the classification that had been previously designated by the pathologists. Blind recategorization of 13 slides was also performed by the same three oral pathologists in order to determine the variability associated with each pathologist's cytologic assessment.

Values obtained from the five classifications were statistically evaluated. Intergroup averages and ranges were derived and a Student's t test was used for comparing unrelated groups.

RESULTS

The calculated average ratios of nucleus to cytoplasm areas by class were as follows: Class I: 3.6%; Class II: 8.1%; Class III: 14.1%; Class IV: 12.8%; and Class V: 23.8% (Figure 3). Calculated ranges of nuclear to cytoplasmic ratios were: Class I: 2.6 to 4.5%; Class II: 6.0 to 10.0%; Class III: 9.6 to 10.5%; Class IV: 10.3 to 15.2%; and Class V: 14.3 to 33.2% (Figure 4).

Interclass statistical evaluation demonstrated that Classes I and II were distinct from all other classes ($p < 0.05$). Classes III and IV were indistinguishable from each other, but were distinct from Class V ($p < 0.10$) (Table 1).

Blind recategorization (Table 2) demonstrated the variation between the three pathologists' categorization of specimens. All of the pathologists agreed on the original classification on slides 10 and 12 only, with no correct recategorization of the Class V slides introduced (numbers 12 and 13). Recategorization of slides 12 and 13

ranged from Class II (pathologist 2) to Class IV (pathologist 1). The Class IV slides (numbers 6, 7, 8, 9, 10, and 11) were recategorized from Class II (pathologists 1 and 2) to Class IV (pathologists 2 and 3). The Class III slides (numbers 3, 4, and 5) generally were recategorized correctly, however, variability was evident, with recategorization ranging from Class II (pathologists 1 and 2) to Class V (pathologist 3). Class I slides (numbers 1 and 2) were recategorized from Class I (pathologist 2 on slide number 2) to Class III (pathologist 2), with pathologists 1 and 2 recategorizing both slides as Class II.

DISCUSSION

Based on the "fuzzy" nature of the intergroup borders associated with Classes III, IV, and V, a three-category system of oral cytologic classification is recommended as an alternative to the five-category system that commonly is employed. The three classes would be: Class I - Normal; Class II - Suspicious; and Class III - Malignant.

Results from this study indicate that when limiting the evaluation of cells to one parameter (i.e., the nuclear to cytoplasmic ratio), significant separation of cell status (i.e., normal versus abnormal) was possible. Classes I and II were distinct from all the other classes (Table 1); whereas Classes III and IV were indistinguishable from each other. They were, however, distinct from Class V. This indicates that computerized evaluation would be a valuable aid

for discrimination between normal, suspicious, and malignant cells. The cytologist could have specific values associated with the nuclear to cytoplasmic ratios indicative of each class. A standardized classification system having specific class values could eliminate or drastically reduce possible inter-examiner variability as was evident in the three pathologists' blind recategorization (Table 2).

The amount of time needed to accomplish 2500 measurements was approximately four hours. Specific software for nuclear to cytoplasmic ratio measurements could reduce the measuring time and result in a convenient system for cytologically evaluating large volumes of specimens in an accurate and precise manner.

MILITARY DISCLAIMER

The commercial materials and equipment are identified in this report to specify the investigative procedures. Such identification does not imply recommendation or endorsement or that the materials and equipment are necessarily the best available for the purpose. Furthermore, the opinions expressed herein are those of the authors and are not to be construed as those of the U. S. Army Medical Department.

LEGENDS

FIGURE 1. a. Class I - only normal cells.

b. Class II - normal, some atypical cells.

c. Class III - uncertain, normal, and abnormal cells.

d. Class IV - borderline to cancer.

e. Class V - cancer.

FIGURE 2. Schematic of image analysis system.

FIGURE 3. Average nuclear to cytoplasmic ratio.

FIGURE 4. Range of nuclear to cytoplasmic ratios.

LEGENDS

FIGURE 1. a. Class I - only normal cells.

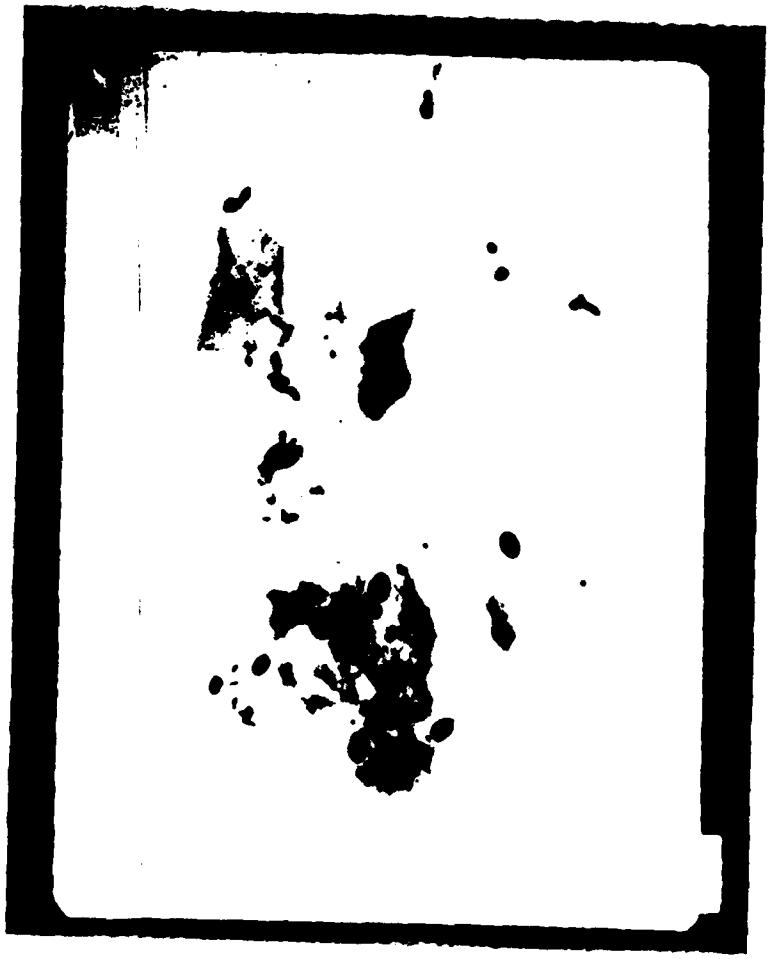


FIGURE 1. b. Class II - normal, some atypical cells.

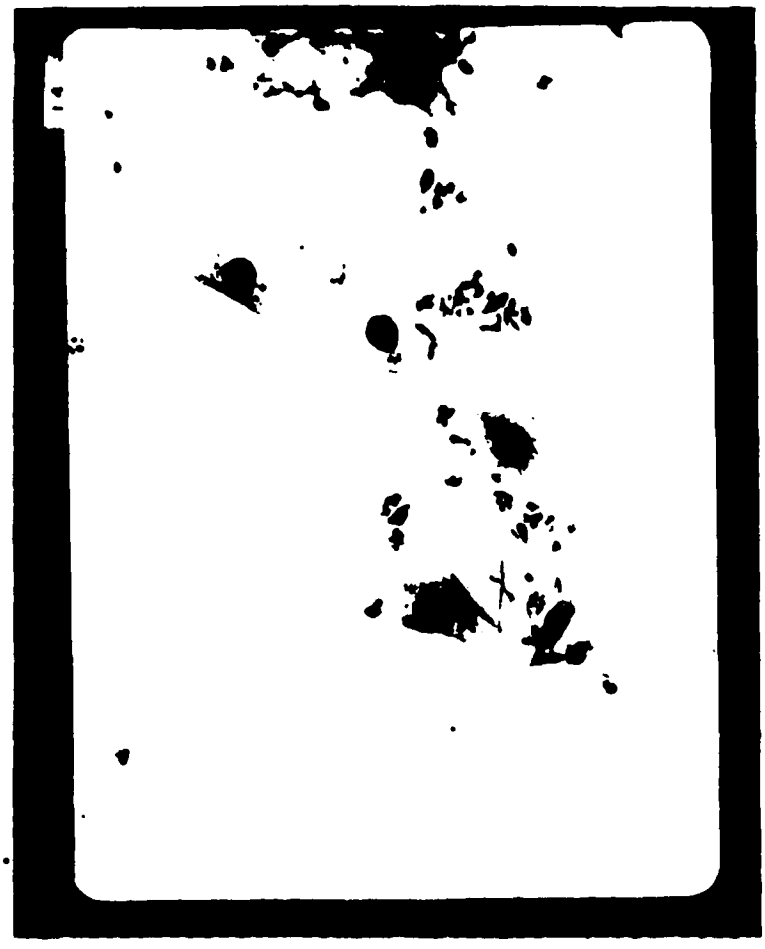
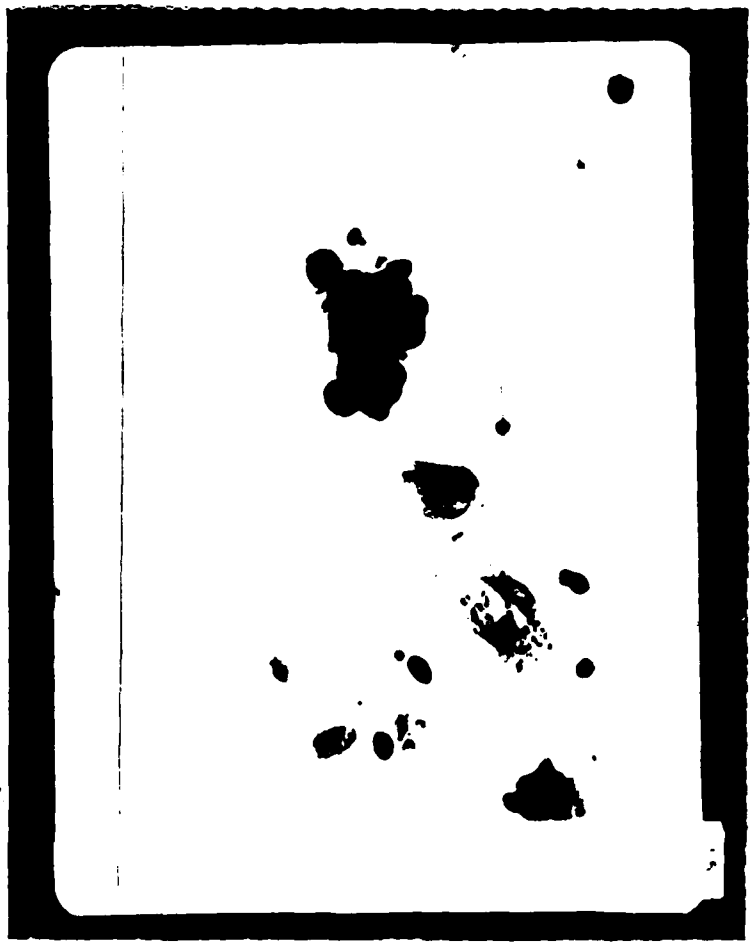


FIGURE 1.

c. Class III - uncertain, normal, and abnormal cells.

FIGURE 1.  cells.

d. Class IV - borderline to cancer.

FIGURE 1.

e. Class V - cancer.

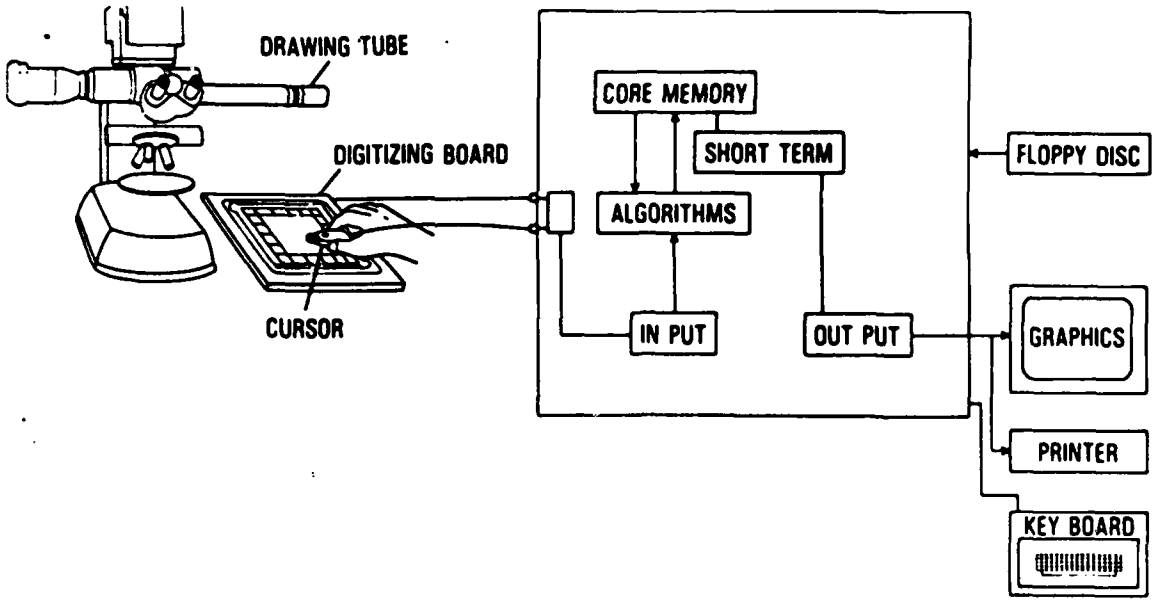
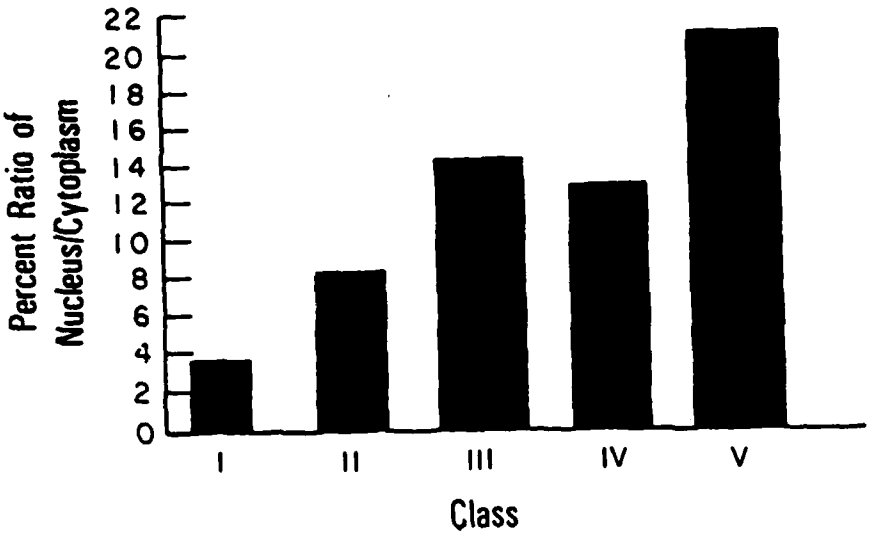
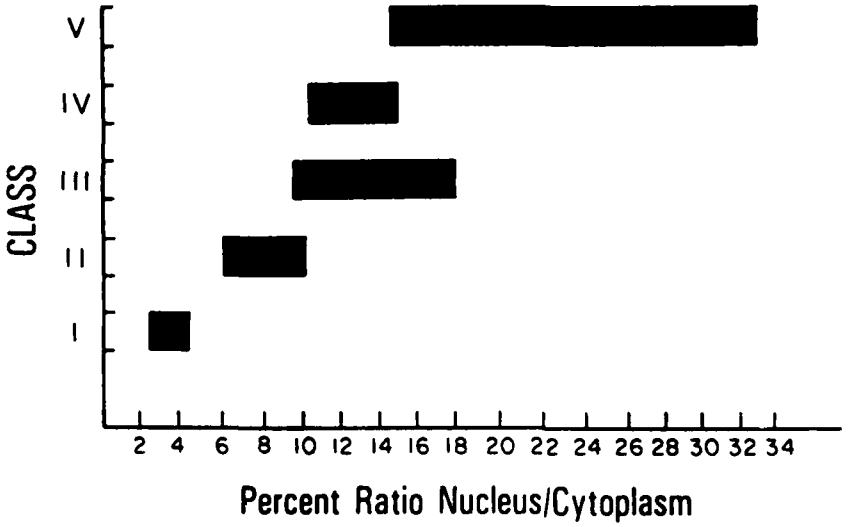


FIGURE 2. Schematic of image analysis system.



al cells.

FIGURE 3. Average nuclear to cytoplasmic ratio.



ırmal cells.

FIGURE 4. Range of nuclear to cytoplasmic ratios.

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TABLE I

CATEGORIZATION ACCORDING TO NUCLEAR:CYTOPLASMIC RATIOS

	CLASS I	CLASS II	CLASS III	CLASS IV	CLASS V
CLASS I	X	0.05	0.05	0.05	0.05
CLASS II	0.05	X	0.05	0.05	0.05
CLASS III	0.05	0.05	X	A	0.10
CLASS IV	0.05	0.05	A	X	0.10
CLASS V	0.05	0.05	0.10	0.10	X

$p < 0.05$
$p < 0.10$

A = No different

TABLE II

RECATEGORIZATION BY PATHOLOGISTS OF 13 SPECIMENS

SLIDE #	ORIG. CATEGORY	PATH. 1 RECAT.	PATH. 2 RECAT.	PATH. 3 RECAT.
1	I	II	III	II
2	I	II	I	II
3	III	III	III	V
4	III	III	III	V
5	III	II	II	V
6	IV	II	IV	V
7	IV	II	IV	III
8	IV	III	IV	IV
9	IV	II	II	III
10	IV	IV	IV	IV
11	IV	IV	IV	IV
12	V	IV	II	III
13	V	III	II	III


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